

Lycopene and cardiovascular disease¹⁻³

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ABSTRACT Considerable evidence suggests that lycopene, a carotenoid without provitamin A activity found in high concentrations in a small set of plant foods, has significant antioxidant potential in vitro and may play a role in preventing prostate cancer and cardiovascular disease in humans. Tomato products, including ketchup, tomato juice, and pizza sauce, are the richest sources of lycopene in the US diet, accounting for >80% of the total lycopene intake of Americans. Unlike other carotenoids, lycopene is not consistently lower among smokers than among nonsmokers, suggesting that any possible preventive activity is not as an antioxidant. Instead, lycopene may have a cholesterol synthesis-inhibiting effect and may enhance LDL degradation. Available evidence suggests that intimal wall thickness and risk of myocardial infarction are reduced in persons with higher adipose tissue concentrations of lycopene. The question of whether lycopene helps to prevent cardiovascular disease can only be answered by a trial specifically evaluating its effectiveness in this area. *Am J Clin Nutr* 2000;71(suppl):1691S-5S.

KEY WORDS Lycopene, cardiovascular disease, carotenoid, antioxidant, LDL

INTRODUCTION

Lycopene is a hydrocarbon carotenoid that has recently received attention for its potential role in preventing prostate cancer and cardiovascular disease in humans. Although similar in structure to the more studied β -carotene, lycopene does not have provitamin A activity. The many conjugated double bonds of carotenoids make them potentially powerful antioxidants, and lycopene is no exception. Indeed, in 1989 Di Mascio et al (1) showed that lycopene had the strongest singlet oxygen-quenching capacity of several carotenoids, with α -carotene, β -carotene, and lutein next in capacity. The weakest singlet oxygen quencher of the antioxidants studied was α -tocopherol, which is found in much greater concentrations in many body systems. In the past, this difference in concentration drew attention away from the carotenoids as antioxidants, and carotenoids have been studied in detail only recently.

Largely because it can be converted to vitamin A, β -carotene has been the most intensely studied carotenoid to date. A significant accumulation of observational evidence suggesting that β -carotene, or foods rich in β -carotene, may protect against cancer led to several clinical trials involving β -carotene supplementation (2, 3). However, these trials showed that β -carotene supplementation either increased or had no effect on the risk of lung cancer in high-risk subjects (4-6).

The deleterious effects of β -carotene supplementation are not restricted to lung cancer. Rapola et al (7) found that persons consuming β -carotene supplements had a 75% increase in fatal coronary heart disease in a comparison with persons not receiving supplements. These researchers found a borderline-significant increase in total coronary events in the β -carotene-supplemented group but no significant increase in nonfatal coronary events.

Although the results of observational studies seem to suggest that intake of foods rich in β -carotene (ie, fruit and vegetables) protects against such chronic diseases as cancer and cardiovascular disease, clinical trials have not found β -carotene to be protective and, in some cases, have even shown a negative effect. This suggests that carotenoids other than β -carotene may be important in preventing disease or that β -carotene is acting through some mechanism beyond that of antioxidation.

FOOD SOURCES AND ABSORPTION OF LYCOPENE

Lycopene is a fat-soluble pigment that gives tomatoes, guava, pink grapefruit, watermelon, and a limited number of other foods their red color. More than 80% of the US dietary intake of lycopene is estimated to come from tomato sources, including ketchup, tomato juice, spaghetti sauce, and pizza sauce (8).

Tomatoes also contain a significant amount of β -carotene. In fact, they are the fourth-leading contributor to provitamin A and vitamin A intake in the American diet (9). Tomatoes are also rich in folate and potassium, and there is almost 3 times as much vitamin C as lycopene in a tomato. Thus, in studies of health benefits of tomatoes, one must consider that they are also rich in nutrients other than lycopene.

The mechanism of absorption of lycopene is not completely understood. Studies have shown that lycopene from tomato products appears more readily in the circulation if the tomato is heated and if a source of fat is included with the meal. Plasma lycopene concentrations increased only slightly in a group receiving 180 g tomato juice (containing 12 mg lycopene) daily for 6 wk (10). This finding is supported by other studies show-

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²Presented at the 17th Ross Research Conference on Medical Issues, held in San Diego, February 22-24, 1998.

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TABLE 1

Lycopene concentrations by smoking status

Authors	Sample	n	Lycopene concentration	Lycopene dietary intake	Factors controlled for in analyses
			nmol/L	μg	
Pamuk et al (19)	African American women, 30–69 y old, serum concentrations	50 nonsmokers 41 smokers	348 ¹ 257 ³	44.2 ± 8.1 ² 31.6 ± 9.0	Age, energy intake, nutrient intake, supplement intake, alcohol intake, medication, BMI, serum cholesterol and serum triacylglycerols
Peng et al (24)	Healthy whites, 26–82 y old, plasma concentrations	62 nonsmokers 34 smokers	606 ± 257 ² 606 ± 312	Data not shown	Age, sex, diet intake estimates, and vitamin supplement use
Brady et al (25)	Men and women, ≥ 50 y old, serum concentrations	186 never smokers 133 past smokers 81 current smokers	418 (384, 456) ⁴ 441 (402, 483) 443 (393, 500)	320 (280, 366) 366 (327, 410) 233 (166, 326)	None
Rao and Agarwal (26)	Healthy men and women, 25–40 y old, serum concentrations	? nonsmokers ? smokers	573.53 ± 107.51 ⁵ 593.98 ± 98	Data not shown	Subjects matched by age and sex
Driskell et al (27)	Men, 25–55 y old, plasma concentrations	10 nonusers 23 smokers 11 tobacco chewers	692 ± 369 ² 545 ± 311 760 ± 637	1403 ± 3300 1021 ± 1264 1963 ± 3345	None
Hininger et al (28)	Healthy men and women, 25–45 y old, plasma concentrations	11 nonsmokers 11 smokers	610 ± 300 ² 560 ± 240	Data not shown	None

¹Geometric mean.² $\bar{x} \pm$ SD.³Significantly different from nonsmokers, $P = 0.03$.⁴Geometric mean; 95% CI in parentheses.⁵ $\bar{x} \pm$ SEM.

ing negligible or only slight increases in plasma lycopene concentrations after consumption of various amounts of unheated tomato juice (11, 12). In one study, however, when heated tomato juice mixed with oil was consumed, serum concentrations of lycopene increased, with a peak 24–48 h after ingestion (12). Similarly, Gartner et al (13) found that concentrations of lycopene in the chylomicrons of 5 human subjects increased ≈ 3 times as much when they consumed tomato paste as when they consumed raw tomatoes. Thus, the availability and absorption of lycopene depend on the processing and treatment of the food that contains the carotenoid and on the fat content of the meal in which lycopene is consumed.

Because of the abundance of double bonds in its structure, there are potentially 1056 different isomers of lycopene, but only a fraction are found in nature (14, 15). The *all-trans*-configuration is the usual form of carotenoids, including lycopene, in foods (8). However, Stahl et al (16) found that heating tomato juice resulted in *trans*-to-*cis* isomerization of lycopene, and on ingestion of this juice, the *cis* isomers of lycopene appeared to predominate in human serum over the *all-trans* isomers. Results from the study by Gartner et al (13) showed that more than half of total lycopene in human serum is in the *cis* form. At present, the exact functions and relative activities of these different isomers are unknown.

LYCOPENE AND SMOKING

Cigarette smoking is a well-known risk factor for coronary atherosclerosis. One theory of its mechanism of action is that smoke introduces a source of free radicals into the body, which cause LDL oxidation, leading to foam cell production and atherogenesis. Studies suggest that the severity of atherosclerosis is related to heightened susceptibility of LDL to oxidation (17). Thus, antioxidants that can protect LDL from oxidation may also protect

humans against coronary heart disease. Smokers have been shown to have lower plasma concentrations of most carotenoids (by 18–44%) than nonsmokers (18–21). In the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, subjects who smoked the most (≥ 20 cigarettes/d) generally had lower serum carotenoid concentrations than did those who quit smoking or smoked < 20 cigarettes/d (22). The relation between smoking and serum concentration of lycopene was not consistently inverse, however.

Human plasma directly exposed to gas-phase cigarette smoke for 9 h showed an 80% decline in lycopene concentration (23). The order of depletion of dietary antioxidants was as follows: lycopene $>$ α -tocopherol $>$ *trans*- β -carotene $>$ lutein/zeaxanthin = cryptoxanthin $>$ γ -tocopherol = retinol. In an observational study ($n = 91$), Pamuk et al (19) found that African American female smokers had 26% lower serum lycopene concentrations than did nonsmokers after adjustment for dietary intake of lycopene and other potential confounders.

The design and results of the study by Pamuk et al are summarized in **Table 1** (19), as are 5 other studies in which no effect of smoking on plasma lycopene concentrations was found. Peng et al (24) found that plasma concentrations of β -carotene, α -carotene, lutein, zeaxanthin, cryptoxanthin, and *cis*- β -carotene, but not lycopene, were lower in smokers than in nonsmokers even at the same level of intake. In another study, Brady et al (25) found that serum lycopene was not significantly lower in smokers than in nonsmokers, even though dietary intake of lycopene was lower in smokers. Rao and Agarwal (26) also reported that serum lycopene concentrations did not differ significantly between nonsmokers and habitual smokers. In a sample of men aged 25–55 y, no significant differences in plasma lycopene concentrations were observed between smokers, tobacco chewers, and nonusers (27). Hininger et al (28) also found no significant difference in

plasma lycopene concentrations between a sample of 11 smokers and 11 nonsmokers. Thus, there is evidence that smoking status is not inversely related to circulating concentrations of lycopene in humans.

Rao and Agarwal (26) studied the effect of smoking and diet on serum lycopene concentrations in humans. Postprandial serum concentrations of lycopene were always lower than fasting serum lycopene concentrations, suggesting the use of lycopene to combat a meal-induced metabolic stress. Similarly, serum lycopene concentrations decreased by an average of 40% immediately after subjects smoked 3 cigarettes in 30 min. A corresponding increase in TBARS (thiobarbituric acid-reactive substances, a measure of lipid oxidation) of the same proportion supports an antioxidant function of lycopene *in vivo*. Thus, the results are mixed, and the relation between lycopene and smoking is not clearly understood.

BIOLOGICAL ACTIVITY OF LYCOPENE

Several studies examined the relation between dietary intake of antioxidants and lipid peroxidation to try to determine which antioxidants may play a role in preventing cardiovascular disease. The hydrocarbon carotenoids, including β -carotene and lycopene, are transported primarily in LDL, which puts them in prime position to protect LDL from oxidation (29).

Steinberg and Chait (30) found that supplementing smokers' diets with an antioxidant-rich tomato-based juice for 4 wk resulted in significantly increased conjugated diene (CD) lag time, decreased CD propagation rate, and decreased breath pentane excretion compared with that in subjects given a placebo juice. Although it is impossible to separate the effects of lycopene from those of the other antioxidants added to the juice, the authors suggested that lycopene intakes correlated most closely with inhibition of LDL oxidation.

In another intervention study, 22 subjects (11 smokers, 11 nonsmokers) consumed a diet with increased fruit and vegetables, supplying ≈ 10 mg β -carotene, 10 mg lycopene, and 10 mg lutein daily for 2 wk (28). The investigators observed an increase in CD lag time of 14% in smokers and 28% in nonsmokers after the supplementation. Again, these results cannot be attributed to lycopene alone, but they contribute to the evidence that carotenoids may protect against diseases related to oxidative stress.

Romanchik et al (31) isolated LDL samples from 5 persons and enriched them with β -carotene, lycopene, and lutein to determine whether this would have an effect on LDL oxidation. On copper-mediated oxidation of the LDL, the carotenoids were destroyed before substantial amounts of lipid peroxidation products were formed, providing further evidence that these pigments may be working as antioxidants. Although lycopene was the most rapidly destroyed of the carotenoids studied, only the LDL enriched with β -carotene exhibited increased CD lag time. In a separate study of LDL from 11 different persons, the same researchers actually found increased oxidation of LDL (as measured by the ferrous oxidation–xylene orange assay) on enrichment with lycopene and lutein, indicating that the relation between lycopene and LDL oxidation is complex (32).

An intriguing nonantioxidant function of lycopene was shown *in vitro* and in humans. Fuhrman et al (33) showed that the addition of lycopene to macrophage cell lines decreased cholesterol synthesis and increased LDL receptors. Incubation with lycopene *in vitro* resulted in a 73% decrease in cholesterol synthesis, which was greater than that achieved with β -carotene. Also, lycopene resulted

in a 34% increase in LDL degradation in the cells themselves and approximately a 110% increase in the removal of LDL from the circulation. To test their finding in humans, the investigators fed 6 men 60 mg lycopene/d for 3 mo (approximately equivalent to the amount of lycopene in 1 kg tomatoes). They found a 14% reduction in plasma LDL cholesterol with no significant change in HDL cholesterol. Based on the calculations of Peto et al (34) that there is a 3:1 ratio between lowering of cholesterol and reduction in the risk of myocardial infarction, we would expect an ≈ 30 –40% reduction in risk in persons consuming this amount of lycopene regularly.

EPIDEMIOLOGIC EVIDENCE FOR A PROTECTIVE EFFECT OF LYCOPENE ON RISK OF HEART DISEASE

The relation between β -carotene and cardiovascular disease has been examined in several studies, including clinical trials involving β -carotene supplements, but in only a few has the association between lycopene intake or biomarkers and risk of this disease been examined (35). The study design and results of the 2 studies in which the association between circulating concentrations of carotenoids and risk of heart disease were examined are summarized in **Table 2**. In addition, the table includes the same information from the 2 other studies in which adipose tissue samples from the European Study of Antioxidants, Myocardial Infarction, and Cancer of the Breast (EURAMIC) were used to examine the relation between tissue concentrations of lycopene and myocardial infarction.

In 1994, Street et al (36) conducted a nested case-control study examining serum carotenoid concentrations that were measured 7–14 y before the onset of myocardial infarction. Although there appeared to be an increased risk of myocardial infarction in the lowest quintile of serum lycopene concentration, there was not a dose-response relation and the trend was not statistically significant. Serum β -carotene concentrations, however, were significantly and inversely associated with risk of myocardial infarction. After stratifying the results by smoking, the authors found that this relation was limited to smokers only. The Atherosclerosis Risk in Communities study measured carotid intima-media thickness (IMT) as an indication of asymptomatic early atherosclerosis in 231 subjects, and 3 y later measured serum antioxidant concentrations in the same persons (37). Although the relation was not significant, persons with higher serum lycopene concentrations had decreased odds of being in the 90th percentile of IMT. β -Cryptoxanthin and lutein plus zeaxanthin were the only carotenoids that had a significant inverse association with carotid IMT.

Using data from the Malaga center of the EURAMIC study of antioxidant concentrations in adipose tissue and incident myocardial infarction, Gomez-Aracena et al (38) found that the risk of myocardial infarction was 60% lower (odds ratio: 0.39, 95% CI: 0.13, 1.19; *P* for trend: 0.04) for the highest quintile of adipose lycopene concentration than for the lowest quintile after adjustment for age, family history of coronary heart disease, and cigarette smoking. The results of the total multicenter, multinational EURAMIC data set confirmed this effect. Men with the highest concentrations of lycopene in their adipose tissue biopsy had a 48% reduction in risk of myocardial infarction when they were compared with men with the lowest adipose lycopene concentrations (39). For each quintile increase in lycopene concentration, there was a significant decrease in myocardial infarction risk. This association was partially


TABLE 2

Lycopene and cardiovascular disease: the epidemiologic evidence

Authors	Study design	n	Lycopene measurement	Outcome	Odds ratio (95% CI)	P for trend	Factors controlled for in analyses
Street et al (36)	Nested case-control study	123 cases, 246 controls	Serum sample	Myocardial infarction	0.75 ¹ (CI not shown)	0.54	None
Iribarren et al (37)	Case-control study (ARIC study)	231 cases, 231 controls	Fasting serum sample	Intima media thickness	0.81 (0.60, 1.08)	Data not shown	Age, blood storage time, total cholesterol and triacylglycerols, education level, former smoking, current smoking, BMI, ethanol intake, hypertension, diabetes mellitus, and vitamin supplement use
Kohlmeier et al (39)	Case-control study (EURAMIC study)	662 cases, 717 controls	Adipose tissue needle aspiration biopsy	Myocardial infarction	0.52 (0.33, 0.82)	0.005	Age, center, BMI, smoking, family history of disease, and history of high blood pressure
Gomez-Aracena et al (38)	Case-control study (one EURAMIC study center)	100 cases, 102 controls	Adipose tissue needle aspiration biopsy	Myocardial infarction	0.39 ¹ (0.13, 1.19)	0.04	Age, family history of coronary heart disease, and cigarette smoking

¹Odds ratios were inverted for comparability, using the lowest quintile as the referent value.

masked by β -carotene concentrations. When there was simultaneous control for the 3 primary carotenoids, lycopene was the carotenoid with the major effect.

We, also, stratified data from the EURAMIC study by smoking status and examined the association between adipose lycopene concentrations and myocardial infarction. Higher lycopene concentrations tended to be most protective against myocardial infarction in those men who had never smoked (odds ratio: 0.3 for never smokers, 0.4 for exsmokers, and 0.6 for smokers). This result was contrary to what was expected; if lycopene is protective by being an antioxidant, then its effect should be strongest in smokers who are in a high oxidation state. Thus, the idea that lycopene is working by some other mechanism than as an antioxidant needs further examination. We should also continue to consider that tissue concentrations of lycopene may simply be a marker of some other nutrients or phytochemicals in tomatoes that are protecting the body from disease. 

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